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Comprehensive Insights into Neuropsychiatric Systemic Lupus Erythematosus

Diagnostic Advances and Therapeutic Approaches

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, often affecting women of childbearing age, with periods of exacerbations and remissions. SLE can impact multiple organs, causing a range of clinical symptoms. Neuropsychiatric systemic lupus erythematosus (NPSLE) includes symptoms like headaches, seizures, anxiety disorders, cognitive dysfunctions, psychosis, and neuropathies. Its diagnosis is challenging, and treatment is complex.

Purpose: This study aims to explain the pathophysiology of NPSLE, describe diagnostic methods, and summarize current treatment methods based on recent research.

Methods: Databases such as PubMed, Medline, and ResearchGate were used.

State of current knowledge: Early and accurate diagnosis of SLE is crucial for optimal patient management. The 2019 EULAR/ACR classification criteria have improved diagnostic precision with a weighted scoring system for diverse disease manifestations. Therapy of neuropsychiatric lupus focuses on symptom control and causal treatment, considering anti-inflammatory action or counteracting ischemic incidents. It involves immunosuppressive agents and antiplatelet or anticoagulant substances. Non-pharmacological interventions and lifestyle modifications are also important. The dynamic criteria reflect ongoing advancements in understanding SLE, emphasizing continuous research and collaboration.

Conclusions: The diagnosis of NPSLE requires excluding other causes of neuropsychiatric symptoms, such as infections, endocrine disorders, or drug reactions. Diagnostic methods vary based on symptoms, including lumbar puncture, CSF analysis, EEG, cognitive function assessment, and MRI. The treatment of NPSLE focuses on symptom control and causal treatment, with therapy individualized based on symptom severity and patient burden.

KEYWORDS

Neuropsychiatric systemic lupus erythematosus, cognitive dysfunction, antinuclear antibodies

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that most frequently affects women of reproductive age. The disease course involves periods of exacerbation and remission. SLE can impact multiple organs, leading to various symptoms that create a complex clinical picture. Among the general symptoms are fatigue, weight loss, and fever [1]. One of the most commonly affected organs in lupus is the skin. Patients may experience photosensitivity, butterfly-shaped facial rashes, or hair loss [2]. Additionally, swelling and joint pain can occur. SLE may also affect the kidneys, causing inflammation and potentially leading to end-stage renal disease over time [3]. Patients are at an increased risk of developing atherosclerosis. SLE can attack the heart, causing conditions such as pericarditis [2].

In addition to the organs mentioned above, SLE can also affect the nervous system, leading to neurological and psychiatric symptoms, known as Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). NPSLE can affect both the central and peripheral nervous systems. Central nervous system symptoms include headaches, seizure disorders, aseptic meningitis, demyelinating syndromes, anxiety disorders, cognitive dysfunction, acute confusional state, psychosis, and mood disorders. Peripheral nervous system symptoms may include autonomic neuropathy, myasthenia gravis, polyneuropathy, and Guillain-Barré syndrome [4].

RISK FACTORS

The development of SLE is influenced by environmental, hormonal, and genetic factors. Smoking, exposure to silica, use of oral contraceptives, and hormone replacement therapy increase the likelihood of developing the disease, while moderate alcohol consumption reduces its risk. Factors potentially contributing to the development of SLE also include UV radiation, infections (such as the Epstein-Barr virus), air pollution, pesticides, and heavy metals (e.g., mercury). These may increase the risk of the disease, but further research in this area is needed [5]. In the context of the neuropsychiatric form of SLE, genetic factors such as the TREX1 gene and the HLA-DRB1*04 allele are discussed [4].

PATHOGENESIS OF NPSLE

The pathogenic processes leading to the development of neuropsychiatric symptoms in NPSLE are still largely unexplained. However, it is known that many factors are involved in the pathogenesis, including cytokines, autoantibodies, immune complexes, complement activation, blood-brain barrier (BBB) dysfunction, and genetic factors (the genotypes FcγRIIIa, FcγRIIIb, and ITGAM may be associated with NPSLE) [7].

To date, around 20 antibodies present in SLE have been linked to NPSLE. Among the most characteristic autoantibodies in this disease are antiphospholipid antibodies. These include: anticardiolipin antibody (aCL), antiphosphatidylserine antibody (aPS), lupus anticoagulant (LA), and anti-β2 glycoprotein-I antibody (anti-β2GPI). They exhibit prothrombotic effects and can accelerate atherosclerosis, which promotes the occurrence of ischemic foci in the brain [7]. It is believed that these antibodies may influence the development of movement disorders, seizures, chorea, depression, and cognitive dysfunction [9].

Antibodies potentially associated with NPSLE also include antibodies against ribosomal P protein. These antibodies are believed to influence the onset of conditions such as depression and psychosis in patients [9]. Studies have shown that these antibodies bind to a protein present on the surface of neurons, causing an increased influx of Ca2+ into the cell and apoptosis. The action of these antibodies has been primarily observed in brain regions responsible for cognition, memory, and emotions. This is related to the distribution of the surface P protein in these areas [10].

Antibodies against endothelial cells (AECA), which cause damage to blood vessel walls, are also associated with the occurrence of depression and psychosis in patients with SLE [7].

The development of cognitive and depressive disorders may be influenced by antibodies against the N-methyl-D-aspartate receptor (anti-NMDA). Particular attention is given to

antibodies against the 2A subunit of the N-methyl-D-aspartate receptor (NR2A). These antibodies can cause excessive stimulation of glutamate receptors, reduce NMDA receptor expression, and thereby impair their function. An important factor in this context is the degree of blood-brain barrier damage. The greater the damage, the more antibodies penetrate the central nervous system and exert a negative effect on it [7][9].

Recent studies have also shown a link between elevated levels of antibodies against glyceraldehyde 3-phosphate dehydrogenase (anti-GAPDH) and NPSLE. Antibody levels also correlated with increased intracranial pressure and the presence of cerebrovascular changes [11].

Other antibodies observed at elevated levels in patients with NPSLE (compared to those without neuropsychiatric symptoms) include anti-UCH58-69 antibodies. Additionally, these antibodies have been found to correlate with the severity of the disease [12].

The occurrence of NPSLE may also be associated with antibodies against microtubule-associated protein 2 (anti-MAP-2), antibodies against U1 ribonucleoprotein (anti-U1RNP), and antibodies against triosephosphate isomerase (anti-TPI) [9].

In patients with SLE, increased blood-brain barrier (BBB) permeability has been observed compared to healthy individuals. Dysfunction of this barrier allows autoimmune antibodies to enter the central nervous system (CNS), which can cause neuronal damage and thus lead to neuropsychiatric symptoms [7,8]. Inflammatory mediators may contribute to the development of BBB disruption. Some of these mediators can be produced in the subarachnoid space by neurons or glial cells. Among the inflammatory mediators involved in the pathogenesis of NPSLE are IFN-α, IL-6, IL-8, MCP-1, IP-10, and TNF-α. IL-6 is believed to have the strongest positive correlation with NPSLE among cytokines [7].

Additionally, it has been observed that IL-6 levels in both serum and cerebrospinal fluid were significantly elevated in patients with acute confusional state (ACS) compared to NPSLE patients without ACS [13]. IFN-α also attracts considerable interest. It has been noted that some patients undergoing interferon-based therapy developed CNS symptoms such as depression, manic episodes, and seizures. Studies using transgenic mice have shown that high levels of IFN-α in the CNS may be associated with the development of seizures and severe behavioral disorders [14]. Unfortunately, the pathogenesis of NPSLE is very complex, and many aspects remain to be elucidated. More research in this area is necessary.

DIAGNOSIS AND CRITERIA

Systemic lupus erythematosus is a clinically heterogeneous disease with an unpredictable course and numerous flares. Diagnosis is made by careful clinical observation and posing

diagnosis with negative serological tests is not uncommon [14]. The symptoms of SLE result from the presence of multiple autoantibodies, leading to the formation and deposition of immune complexes and other immunological processes [15]. Consequently, the disease typically has a systemic course, and when one organ is predominantly affected, it poses a diagnostic challenge.i It is a difficult disease to diagnose, and classification criteria are essential for identifying patients. Diagnostic criteria, generally broad, must reflect the various features of the disease (heterogeneity) to accurately identify as many individuals suffering from the condition as possible [16].

The current diagnostic criteria are the result of collaboration between the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). They were developed in 2019 and are used worldwide. The 2019 EULAR/ACR classification criteria for SLE include positive ANA at least once as an obligatory entry criterion. That criteria perform better in patients with longstanding disease than in new-onset SLE [17][18].

Entry criterion: the presence of ANA (antinuclear antibodies) at a dilution of 1:80 or higher on HEp-2 cells. If they are absent, no further diagnosis for SLE is pursued. If present, additional criteria are used. A total score of at least 10 from the additional criteria is required for a full diagnosis of SLE. Use of ANA entry criterion, hierarchically clustered, and weighted criteria reflects current thinking about SLE.

Systemic Lupus Erythematosus affects the nervous system causing various manifestations of the central nervous system (CNS) and peripheral nervous system (PNS). We can divide NPSLE (Neuropsychiatric Systemic Lupus Erythematosus) into focal or diffuse. Clinical manifestations may range from subtle cognitive dysfunction to acute confusional states, seizure disorders, and psychosis [19]. These manifestations can precede the onset of lupus or occur at any time during its course. They can occur in the setting of active SLE or during quiescent periods and may present as single or multiple neurologic events in the same individual [20].

The prevalence of NPSLE varies widely according to different series and is estimated to be between 37 and 95% [21]. In a patient with SLE and neuropsychiatric symptoms, it is necessary first to determine whether the symptoms are caused by SLE (the disease process or therapy) or another condition. The diagnostic process initially involves ruling out secondary causes, such as infections, endocrine disorders, or adverse drug reactions. SLE patients with signs suggestive of neuropsychiatric disease should be treated like non-SLE patients presenting with the same manifestations.

Another important recommendation is the choice of test depends upon the type of neuropsychiatric manifestation. For example, to exclude CNS infection use lumbar puncture and CSF analysis, EEG with neuropsychological assessment of cognitive function, NCS, and neuroimaging (MRI) to assess brain structure and function. The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences [22].

The expert committee of American College of Rheumatology (ACR) expert-committee, in 1999 identified 19 neuropsychiatric conditions, termed 'case definitions', in NPSLE patients. These NP syndromes can be divided into 12 central nervous system (CNS) and 7 peripheral nervous system (PNS) [20]. These syndromes are: aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis and connected to PNS - Guillain-Barre syndrome, Autonomic disorder, mononeuropathy, myasthenia gravis, neuropathy, plexopathy, and polyneuropathy.

The neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) is a challenge for clinicians, both at a diagnostic and therapeutic level. In the absence of a diagnostic gold standard for neuropsychological symptoms in lupus, this differentiation is primarily made by excluding other causes [19][20].

THERAPEUTIC APPROACH

Therapy of neuropsychiatric lupus is essentially based on two goals: symptom control and causal treatment, which, depending on the predominant pathophysiological pathway in a given patient, may be based on either anti-inflammatory action or counteracting ischaemic incidents [4][23]. Treatment aimed at symptom control depends on the specific neuro-psychiatric manifestation, regardless of the underlying disease entity, including those outside the lupus classification [24]. These measures include the use of antiepileptic drugs when seizures occur, anxiolytics, antidepressants and antipsychotics as needed. Neurotropic drugs and neuroleptics are used in cases of peripheral nervous system involvement [4].

Causal treatment remains problematic due to the complexity of the pathophysiological sensitive and specific biomarkers [4][25]. It mirrors therapies used in other lupus subtypes, but relatively often remains an empirical intervention. [25][26]. In cases of disease manifestations primarily resulting from an inflammatory response, immunosuppression, i.e. corticosteroids in monotherapy or in combination with other immunosuppressive agents, is recommended, with the aim of stabilising symptoms. For secondary prevention of ischaemic

incidents, antiplatelet and anticoagulant substances are useful [24] [25], especially when antiphospholipid antibodies are found [22]. Some authors suggest combining the two therapies when both pathophysiological pathways coexist [25]. The need for appropriate therapy in relation to the severity of symptoms and the importance of tailoring it individually to the individual patient and his or her burden are also emphasised [25].

Symptomatic treatment

Antiepileptic treatment should be initiated in the presence of risk factors such as: a second seizure episode 24 h after the first, severe brain damage, presence and structural changes on MRI (ang. magnetic resonance imaging), focal neurological symptoms, focal seizures or epilepsy-like patterns on EEG (Electroencephalography).

Generalised convulsions usually respond to treatment with phenytoin or barbiturates, while complex focal convulsions require carbamazepine, clonazepam, valproic acid or gabapentin

Generalised convulsive status epilepticus (GCSE) is a life-threatening condition and requires immediate treatment. Brain imaging should be performed once the patient has been stabilised to assess for structural abnormalities, bleeding or foci of ischaemia. In patients with persistent unconsciousness after GCSE, continuous EEG monitoring (electroencephalography) can be performed to exclude generalised non-convulsive status epilepticus (NCSE) [4][24].

Antiepileptic effects are also shown by antimalarial drugs, as demonstrated in the LUMINA study [18], and further confirmed in another cohort study on 1,631 SLE patients. The mechanism of this association remains unknown [19][27]. On the other hand, antimalarial drugs have been shown to increase the risk of seizures in patients with a history of a seizure episode [28][29].

Antipsychotics in the symptomatic treatment of neuropsychiatric lupus are used when severe symptoms such as psychosis, catatonia or agitation are present. During therapy, the patient should remain under the care of a therapeutic centre for monitoring and treatment in the event of complications such as agranulocytosis, metabolic syndrome, QT prolongation or infection. Treatment should be initiated and discontinued gradually, especially in the event of NPSLE recurrence [24]. The choice of medication depends on the type and severity of symptoms, their pathophysiology, as well as the response to treatment and patient tolerance. Second-generation antipsychotics are preferred to first-generation antipsychotics because of the lower risk of extrapyramidal symptoms and the occurrence of neuroleptic malignant syndrome.

Of the second-generation antipsychotics, clozapine shows the most favourable safety profile in neuropsychiatric lupus, followed by quetiapine. The use of aripiprazole, a partial dopamine receptor agonist, may be beneficial in cases of dopamine deficiency or Parkinson's syndrome [4][30].

Anti-anxiety medication works by altering the action of neurotransmitters in the brain, making them likely to be effective in patients with NPSLE with associated anxiety disorders. The choice of drug should take into account the patient's tolerance, response to treatment, and the spectrum and severity of symptoms [4][31].

Mood stabilisers are recommended by EULAR (European League Against Rheumatism) for the treatment of neuropsychiatric lupus, especially in the event of mood disorders, seizures or psychotic disorders. Studies comparing these guidelines with previously used therapy indicate a more favourable effect when drugs from this group are used [32]. The choice of drug should be preceded by an analysis of the patient's condition, his or her tolerance to the preparation, response to treatment, potential interactions with other drugs and the doctor's experience. Treatment should be in close collaboration between the rheumatologist and the psychiatrist. Commonly used medications include: lithium, antiepileptics and antipsychotics [4][19].

Primary prevention

Antimalarial drugs, i.e. chloroquine, hydroxychloroquine and quinacrine in the treatment of lupus have been used continuously to date since the first reports of its efficacy were published in the 1950s [33]. Hydroxychloroquine at a dose of 200-400 mg/day is recommended throughout the entire period of the disease, irrespective of the severity or intensity of symptoms, even during pregnancy, especially for skin and musculoskeletal symptoms [34].

The use of malarial drugs has been confirmed to reduce mortality in patients with lupus [35], and in addition, through its immunomodulatory effect, is involved in the reduction of cardiovascular incidents [36] by lowering lipidaemia, preventing the development of diabetes and lowering antiphospholipid antibody titres [37][38]. An anticonvulsant effect of these preparations was also observed in the LUMIA study [4][18], which was confirmed in later studies [4]. An anticoagulant effect of 68% reduction of thrombotic events in patients with lupus was also demonstrated in one study [39] , and the findings were confirmed in subsequent studies [40][41].

The typical side effect of chloroquine preparations is retinopathy, which is how they differ from quinacrine [25]. Other less common side effects include dermatitis, gastrointestinal symptoms, leukopenia, thrombocytopenia, aplastic anaemia and co-cardiotoxicity [45]. It has also been shown that these preparations may increase the risk of seizures in patients with previously diagnosed epilepsy [28][29].

Statins

In addition to the well-established hypolipemic effect of statins, competitive hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors [43], it is worth bearing in mind their immunomodulatory effect by inhibiting the secretion of pro-inflammatory cytokines and the adhesion of pro-inflammatory molecules, counteracting intraepithelial cell activation induced by antiphospholipid antibodies, inhibiting T-lymphocyte function and reducing the activity of pro-inflammatory cells on the atherosclerotic plaque [44]. Despite the potential positive effects of statins in patients with SLE, no efficacy has been proven for neither primary nor secondary prevention of cardiovascular events in both adult [45] and paediatric patients [46] . In contrast, it is worth adding that patients with lupus and hyperlipidaemia and/or who are eligible for inclusion of treatment according to the general cardiovascular disease prevention guidelines benefit from statin therapy [47].

Treatment of neuropsychiatric lupus associated with inflammation

Glucocorticosteroids

Glucocorticosteroids (GCS) are widely used in the control of autoimmune diseases, including NPSLE to calm the inflammatory response and prevent organ damage [48]. They act through two main mechanisms. The genomic mechanism involves inhibiting the transcription of genes responsible for inflammatory responses, such as cytokines or chemokines, and increasing the transcription of genes with anti-inflammatory effects, which may include, for example, annexin A1, lipocortin or interleukin 10 [49]. A non-genomic mechanism involves the binding of GCS to membrane receptors, thereby affecting signal transduction pathways such as MAPK, NF-κB, and PI3K/Akt, which modulate the activity of macrophages, T and B lymphocytes and influence their viability, proliferation, differentiation and function [49].

Glucocorticosteroids continue to be a mainstay of causal therapy for neuropsychiatric lupus[25]. It has been shown that for the inflammatory background of SLE, the use of glucocorticosteroids can alleviate neuropsychiatric symptoms in 70% of patients with NPSLE [50]. Psychiatric symptoms that may be due to an autoimmune inflammatory response include

psychosis, acute confusional states or transverse myelitis and can be treated with high doses of steroids or in combination with cyclophosphamide or mycophenolate mofetil. Treatment of recurrent NPSLE with rituximab, intravenous immunoglobulin or plasmapheresis is recommended [4].

GCS preparations differ in their profile of action. The most commonly used in neuro-psychiatric lupus include:

1. Prednisone, activated in the liver from prednisolone. It is characterised by moderate potency and a half-life of 3-4h. In NPSLE, the doses used are 0.5-1 mg/kg/day.
2. Methylprednisone differs from prednisol in its greater potency and longer half-life: 18-36h. It is used in severe neuropsychiatric lupus at a dose of 0.5-1 mg/kg/day.
3. Dexamethasone has a very potent action and a half-life of 36-45h. It is used in relapsing neuropsychiatric lupus at a dose of 10 to 100 mg. [4]

The use of glucocorticosteroids is associated with numerous side effects [50]. These include hypertension, dyslipidaemia, osteoporosis, cataracts, glaucoma, hypokalaemia, peptic ulcer, diabetes, increased risk of infection or latent virus reactivation. The risk factor for the development of complications of steroid therapy is primarily the long duration of use, the total amount of substance ingested is of secondary importance [51] .

The use of glucocorticosteroids can also cause a number of psychiatric side effects, the risk of which increases at doses equivalent to 1 mg/kg/day of prednisone or more [52]. Some patients develop: depression, hypomania and in some patients, due to disruption of the hypothalamic-pituitary axis, a steroid-induced psychosis is observed. This usually occurs up to 8 weeks after the steroid is started or the dose is increased. Steroid-induced psychosis needs to be differentiated from neuropsychiatric lupus due to similar symptoms - the symptoms of psychosis resolve soon after steroid dose reduction, unlike NPSLE [51][52].

Cyclophosphamide

Cyclophosphamide is used in severe forms of SLE to control the underlying inflammatory process. Acts by inhibiting the production of immune complexes, thereby limiting damage to the nervous system [50].

Cyclophosphamide also improves the condition of patients with Guillain-Barré syndrome induced systemic lupus erythematosus, while emphasising the role of careful monitoring and individualisation of therapy with this substance in NPSLE [53][54]. Serious adverse reactions to cyclophosphamide include: post-dose convulsions of unknown mechanism or acute encephalopathy caused by hyponatremia [52].

Azathioprine

Azathioprine is a prodrug that is rapidly converted to mercaptopurine and methylnitroimidazole by thiopurine S-methyltransferase (TPMT) [55]. The mechanism of action of azathioprine is not fully understood. Azathioprine interferes with purine metabolism and inhibits lymphoid cell proliferation after antigenic stinnmulation [56][57].

Purine analogues are cytotoxic and destroy stimulated lymphoid cells; 6-thioguanine triphosphate, a metabolite of azathioprine, modulates the activation of the rac1 protein when co-stimulated with CD28, inducing apoptosis of T lymphocytes [58]. Inhibition of purine metabolism leads to inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis. This results in a reduced immune response, which may help to alleviate the symptoms of NPSLE [4][59].

The positive effects of this drug in patients with SLE, especially in preventing relapses, were described as early as the 1970s [57]. Currently, azathioprine (2-3 mg/kg/day) is mainly used in SLE patients with arthritis symptoms, dermatomucosal changes and serositis, and as maintenance therapy for lupus nephritis [58]. Side effects of azathioprine include bone marrow suppression, hepatotoxicity, gastrointestinal intolerance and a slightly increased risk of infection [59]. In addition, in the absence of TPMT activity, patients are exposed to higher levels of thioguanine nucleotides, which increases the risk of severe, life-threatening myelosuppression; therefore, some authors recommend determining TPMT activity before starting azathioprine therapy [58] .

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a pro-drug of mycophenolic acid, an inhibitor of lymphocyte proliferation that inhibits antibody formation, cellular immune response, expression of adhesion molecules and recruitment of lymphocytes and monocytes to sites of inflammation [60].

Mycophenolate mofetil and mycophenolic acid are administered orally at doses of 1000-3000 mg/day and 1080-1440 mg/day, respectively. The main side effects of mycophenolate mofetil are gastrointestinal intolerance (nausea, abdominal pain, mild to moderate diarrhoea), bone marrow suppression and infections [62] . In NPSLE, mycophenolate mofetil (MMF) was used as an alternative to cyclophosphamide for induction therapy of lupus nephritis. A study comparing the efficacy of MMF with cyclophosphamide in lupus nephritis showed that both drugs were effective, but MMF had a better safety profile [62].

Methotrexate

Metotrexate is a folic acid inhibitor. The drug is very rarely used in NPSLE and the evidence is limited to a few case series reporting the effect of intrathecal administration of methotrexate. Valesini et al. described improvement in three patients with NPSLE after a combination of intrathecal methotrexate and dexamethasone [64]. A similar study has been published in China. A total of 109 patients received a combination of intrathecal methotrexate and dexamethasone (one to five injections), with positive treatment effects [65]. Wang et al. reported an efficacy rate of 89% for treatment with methylprednisolone in combination with intrathecal methotrexate in 36 patients with NPSLE. Despite these results, intrathecal administration of methotrexate is not considered common practice and is limited to a few centres [24].

Cyclosporin A

Cyclosporin A is a calcineurin inhibitor, inhibits T-lymphocyte activity by blocking the transcription of IL-2 and other cytokines, and is used in patients with SLE at daily doses of 2.5-3 mg/kg [65]. Most of the data on these drugs come from experience in the treatment of lupus nephritis. This therapy can cause side effects such as hypertension, deterioration of renal function and hypertrichosis [66]. There are no studies explicitly describing the effect of cyclosporine A on neurological symptoms in SLE. Cyclosporine A, in combination with therapeutic fluid exchange (TPE), was used in 18 patients with NPSLE suffering from organic brain disorders and psychosis. Adding this combination to the current standard therapy, which includes corticosteroids and azathioprine or cyclophosphamide during disease exacerbation, leads to a faster improvement of neurological symptoms. However, the true efficacy of fluid replacement and cyclosporine A remains unknown due to the concurrent use of both therapies [68].

Biologicals

Rituximab, Belimumab and Anifrolumab are used to treat NPSLE [4]. Rituximab is a monoclonal antibody directed against B lymphocytes, which play a key role in systemic lupus erythematosus (SLE). Clinical trials have shown that it can effectively eliminate B lymphocytes and improve clinical outcomes [69].

Belimumab is an immunosuppressive drug that is used as an alternative to cyclophosphamide in the induction therapy of lupus nephritis, showing comparable efficacy and a better safety profile [70].

Anifrolumab is a human monoclonal antibody directed against type I interferon receptor subunit 1, which blocks the action of type I interferons. Two phase 3 studies (TULIP-1 and TULIP-2) and a phase 2b study (MUSE) provide substantial evidence for the efficacy and safety of anifrolumab in moderate to severe SLE. In these studies, monthly intravenous administration of 300 mg of anifrolumab showed treatment differences of >16% compared with placebo after 52 weeks. Evidence from these clinical trials suggests that in patients with active SLE, anifrolumab is more effective than placebo in achieving the composite endpoints of disease activity response and reduction in oral corticosteroids [71].

Treatment of neuropsychiatric lupus associated with ischaemia

Anticoagulants have demonstrated efficacy in the prevention and treatment of venous and arterial thromboembolism; however, their use is also associated with an increased risk of bleeding. This makes their use in primary prevention in patients with SLE remain controversial [72].

In SLE patients with cerebral venous and sinus thrombosis, treatment with oral anticoagulants is recommended. The optimal duration of oral anticoagulant therapy after the acute phase is unclear. Guidelines recommend oral anticoagulation (INR range 2.0-3.0) for 3-6 months, and long-term anticoagulation should be considered in patients with confirmed APS antiphospholipid syndrome.

In some SLE patients with positive aPL antibodies and myelopathy, improvements were reported when anticoagulants were added to immunosuppressive therapy. However, other authors found no additional benefit compared to standard immunosuppression [73].

In SLE patients with chorea or seizures, anticoagulation may be considered in cases of coexisting aPL antibodies, aPL-related optic nerve ischaemic neuropathy and in SLE patients with positive aPL antibodies and cranial neuropathy unresponsive to immunosuppressive therapy. A single study suggests that patients with APS and cognitive dysfunction may benefit from anticoagulation therapy [73][74].

Aspirin

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) that has analgesic, antipyretic, anti-inflammatory and antiplatelet effects. It can be used in NPSLE for the following purposes:

1. Prevention of thrombotic events: Aspirin inhibits the enzyme cyclooxygenase-1 (COX-1), which reduces the production of thromboxane A2, which prevents platelet aggregation. In patients with NPSLE, this reduces the risk of thromboembolic complications [74].
2. Headache treatment: Aspirin has analgesic and anti-inflammatory properties that can relieve headaches, one of the most common symptoms of NPSLE.
3. Modulation of the type I interferon response: Aspirin may have immunomodulatory effects on the type I interferon pathway, which is involved in the pathogenesis of SLE and NPSLE. Aspirin may reduce interferon-stimulated gene expression and levels of interferon-alpha, a cytokine that promotes inflammation and autoimmunity in patients with NPSLE [75][76].

Heparin and Warfarin

Anticoagulant therapies, such as heparin and warfarin, can significantly improve the long-term prognosis of patients with SLE [77] . Heparin is often used as initial treatment, given by injection, and in most cases oral warfarin is then started under INR control, despite less evidence for its use in patients with SLE. However, it has been shown that warfarin (1-5 mg/day) started concurrently with steroid therapy for at least 3 months can prevent the onset of bone necrosis associated with SLE [4][77].

Use of NOACs

New oral anticoagulants (NOACs) are a class of drugs that act as direct inhibitors of thrombin or factor Xa, two key enzymes in the clotting cascade. They are used in the prevention and treatment of thromboembolic disorders such as stroke, deep vein thrombosis and pulmonary embolism [4][24].

NPSLE attributed to a prothrombotic state with antiphospholipid antibodies (aPL) justifies the use of anticoagulants and antiplatelet agents. Anticoagulation may be more effective than antiplatelet therapy in the secondary prevention of thrombotic events in patients on antiphospholipid therapy [4]. Formulations with recognised activity include: Rivaroxaban, dabigatran, apixaban or edoxaban [78][79].

Other treatment proposals and therapy developments:

IVIGs are beneficial in autoimmune diseases due to their immunomodulatory effects by blocking Fc receptors, regulating the complement system or regulating T cells [80].

IVIGs have been shown to reduce serum anti-dsDNA antibody titres, reduce proteinuria and reduce daily steroid requirements. They also have beneficial effects during the maintenance phase, in lupus exacerbations and in refractory cases, but their routine use requires further studies [4][81][82].

Non-pharmacological interventions:

Non-pharmacological interventions play a key role and can help control symptoms, improve patients' quality of life and potentially influence the course of the disease. However, specific non-pharmacological interventions for NPSLE are not well documented in the literature. In general, non-pharmacological interventions for autoimmune diseases such as SLE often include lifestyle modifications such as regular exercise, a balanced diet, adequate sleep and stress management techniques [4].

Physical exercise includes aerobic, resistance and stretching activities. They may have beneficial effects on health-related quality of life (HRQoL) but also on disease activity, fatigue, depression, pain and inflammatory markers in patients with SLE. As in the general population, they may also prevent cardiovascular complications [4].

A balanced diet and adequate quality of sleep. Nutrients obtained through a balanced diet are essential for growth, cell function, tissue development, energy and immune defence. They play their role in innate immunity and inflammation by regulating the expression of TLRs (Toll-like receptors), as well as pro- and anti-inflammatory cytokines, thereby influencing immune cell communication and signalling [83][84].

Sleep has also been linked to immune system function. The study showed that sufficient sleep influences the development and differentiation of monocytes [85][86].

Stress management techniques: The so-called 'fight or flight' response increases the reactivity of the immune system. It is linked to PBMC (peripheral blood mononuclear cell) expression profiles related to immune defence and recovery and regeneration [87].

Psychoeducational interventions: These are programmes combining elements of cognitive behavioural therapy, group therapy and education to improve memory, daily functioning and quality of life for SLE patients with cognitive dysfunction or mild neuropsychiatric symptoms. They can also reduce depression, anxiety and fatigue [88].

Complementary and alternative medicine is a broad category encompassing various modalities such as acupuncture, massage, herbal medicine, yoga and meditation. CAM can provide relief from neuropsychiatric symptoms such as headache, mood disorders and anxiety, as well as improving health-related quality of life (HRQoL) [89].

Laser treatment/phototherapy. This technique uses light energy to stimulate tissue healing, reduce inflammation and modulate pain, which can be useful for NPSLE patients with skin lesions and oral ulcers [90].

Other molecules that improve healing and reduce inflammation include hyaluronic acid, vitamin C and curcumin. Hyaluronic acid is a natural component of the extracellular matrix that promotes wound healing by increasing cell migration and proliferation. Vitamin C is an antioxidant involved in collagen synthesis and improves wound healing. Curcumin, a natural anti-inflammatory compound found in turmeric, reduces inflammation and improves wound healing [91][92].

CONCLUSIONS

Conclusions Systemic lupus erythematosus (SLE) is a disease involving multiple organs, causing various symptoms and presenting a complex clinical picture. Typically the disease has a systemic course; however, if a single organ is predominantly affected, it poses diagnostic challenges. Neuropsychiatric systemic lupus erythematosus (NPSLE) occurs with a frequency ranging from 37% to as high as 95% and causes numerous symptoms such as headaches, aseptic meningitis, psychosis, mood disorders, or peripheral neuropathies. The pathogenic processes leading to the emergence of neuropsychiatric symptoms remain unexplained; nevertheless, approximately 20 antibodies, including antiphospholipid antibodies, have been linked to the pathogenesis of NPSLE. The diagnostic process largely relies on excluding secondary causes. Treatment of NPSLE focuses on symptomatic treatment (antiepileptic, antipsychotic, anti-anxiety drugs, and mood stabilisers) and primary prevention (based on immunosuppressive treatment, antiplatelet and anticoagulant drugs). No less

important is non-pharmacological interventions which can help control symptoms. Patients suffering from this complex disease require a careful diagnostic process and treatment.

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